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Abstract

The conditions required for effective immune responses, are outlined. Endocrine and environmental factors that can lead to persistent elevation of inflammatory responses are described. Aging can play a role in facilitating such disproportionate activity. The nervous system is especially vulnerable to prolonged immune events. In addition of being a target for inflammation associated with neurodegenerative disease, the nervous system is also impacted by systemic immune disturbances. Various means allow immune information to access the CNS. Some possible reasons underlying the common occurrence of hyperreactivity of the immune system are considered, together with a few potential ways of addressing this issue.

Keywords	Neurodegeneration: Neuroinflammation, Immune, Microglia, Astroglia,Macrophage, Aging
Taxonomy	Immunomodulation, Inflammation, Neuro-Immune Interactions
Corresponding Author	Stephen Bondy
Corresponding Author's Institution	Center for Occup. and Env. Health,Dept. of Medicine
Order of Authors	Stephen Bondy
Suggested reviewers	Joseph Bobic, Debomoy Lahiri, Anumantha Kanthasamy, Syed Ali, Kedar Prasad

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OCCUPATIONAL AND ENVIRONMENTAL HEALTH
DEPARTMENT OF MEDICINE
100 THEORY, SUITE 100
IRVINE, CA 92617-1830

Dr. Michael K. Racke
Editor-in-Chief
Journal of Neuroimmunology

January 21, 2020

Dear Professor Racke

After receiving comments from reviewers, I am submitting to you a revised version of the manuscript entitled “Aspects of the Immune System that Impact Brain Function”.

The changes that have been made in response to these reviews are listed on the appropriate attachment. I hope that some of the suggestions have resulted in a strengthened manuscript.

I would be grateful for your consideration of this revised version for publication in the *Journal of Neuroimmunology.*

Sincerely,

S C Bondy

Stephen Bondy, Ph. D.
Professor

Changes made in response to comments of reviewers

Reviewer 1

1] The following section is well written: 3.3.2. Slowing onset genetic changes characterizing aging. The author argues in favor of the "use of inexpensive agents such as melatonin, which has been shown to reverse many of the age-related changes modification of the gene expression profile". Here it is important to mention the work showing melatonin level is itself decreasing with age. Refs:
Age-related changes in serum melatonin in mice: higher levels of combined melatonin and 6-hydroxymelatonin sulfate in the cerebral cortex. J Pineal Res. 36(4):217-23. The MT2 melatonin receptor subtype is present in human retina and decreases in AD, Curr Alzheimer Res. 4(1):47-51. Dietary supplementation with melatonin reduces levels of amyloid beta-peptides in the murine cerebral cortex. J Pineal Res. 36(4):224-31.

Response Two references suggested (Lahiri et al., 2004a,b) are now added and discussed in text

2] Section: 2.2.4 Environmental factors: This is an important are. The author should provide a "big picture" of the human disease, particularly as complex as AD. Refs: Epigenetics of dementia: understanding the disease as a transformation rather than a state. Lancet Neurol. 15(7):760-74; Mol. Psychiatry 14(11):992-1003; Curr Alzheimer Res. 9(5):563-73. --Role of environmental contaminants in the etiology of AD. Curr Alzheimer Res.12(2):116-46.

Response The reference suggested, (Yegambaran et al.,2015) is added. In addition, a reference to the role of abnormal epigenetic profiles in neurodegenerative events, is included (Lardenoije et al., 2015).

3] Re the topic of Immunotherapy, Bondy may consider on touching these points. An inflammation-related nutrient pattern is associated with both brain and cognitive measures in a multiethnic elderly population'. Yu G et al. CAR. 5(5): 493–501. - IVIG treatment exerts antioxidant and neuropreservatory effects in preclinical models of Alzheimer's disease. Counts et al. J Clin Immunol. 2014;34 Suppl 1:S80-5.

Response A new subsection containing 4 additional references has been added (3.3.4) on immunotherapy. A suggested, the reference on diet and inflammation (Gu et al., 2018), is added to the section on diet 3.3.3.

Reviewer 2

Please include astroglia in the key words

Response This has been done

2.1.1. Intensity can allow is repeated in the last line.

Response This error is corrected.

Regarding the meningeal lymphatic system, it is necessary to include a reference supporting this important point.

Response An appropriate reference is added (De Mesquita et al., 2018).

3.1 It is not so clear than microglia are derived from systemic monocytes despite single cell RNA sequence studies (Goldman et al.,2016; Ginhoux and Garel 2018); please, moderate the sentence. In the same line the last sentence, "the proportion of cerebral microglia (microglia is always cerebral) of systemic origin is elevated in some neurodegenerative pathologies…" is not unequivocally demonstrated.

Response. The sentence "However, single-cell RNA sequencing has found that some of these are derived from systemic monocytes" has been altered to "However, single-cell RNA sequencing has provided results suggesting that some of these are derived from systemic monocytes". This is now more suggestive than definitive.

3.2.3. Astroglia
That astrocytes can clear cell dead and "kill microorganisms" needs a reference. That astrocytes can act as real APCs have been a hot debate matter for a long time.

Response A reference describing astroglial autophagy is added (Lui et al., 2018), and the reference to Shechter and Schwartz (2013), is removed. The issue of whether astroglia can kill micro-organisms has been removed, as it is a large area in itself. A reference is also added concerning the likelihood of astroglia acting as viral reservoirs and thus enhancing viral survival in the brain (Li et al., 2016).

Highlights

- Effective immune responses involve well targeted specificity, appropriate duration, and relevant strength.

- Many slow, progressive disease states are consequent to failure of one or more of these critical factors.

- The most common immune failure is excess inflammation either irrelevant, or extended beyond its useful phase. The prevalence of this apparent shortcoming may relate to the increased the longevity of modern times.

- The nervous system has a distinctive vulnerability to excess inflammatory activity, both intrinsic and of systemic origin, which progresses with age.

The conditions required for effective immune responses to viral or bacterial organisms and chemicals of exogenous origin and to intrinsic molecules of abnormal configuration, is briefly outlined. This is followed by a discussion of endocrine and environmental factors that can lead to excessive continuation of immune activity and persistent elevation of inflammatory responses. The role of aging events in facilitating such disproportionate activity, is considered. The specific vulnerability of the nervous system to prolonging immune events is emphasized.

In addition of being a target for inflammation associated with neurodegenerative disease, the nervous system is also seriously impacted by systemically widespread immune disturbances. The means by which immune information can access the CNS and the varying types of activation of those cells that regulate immune responses within the brain are discussed. Some possible reasons underlying the relatively common occurrence of derangement and hyperreactivity of the complex immune system are considered, and a few potential ways of addressing this common problem receive mention.

Aspects of the Immune System that Impact Brain Function

Stephen C. Bondy
Center for Occupational and Environmental Health, Department of Medicine, University of California, Irvine, California 92617, USA

Correspondence to:
Stephen C. Bondy, Ph. D.
Center for Occupational & Environmental Health
Department of Medicine
University of California, Irvine
100 Theory, Suite 100
Irvine, CA 92617-1830
USA
Tel: 1-949-824-8077
scbondy@uci.edu

Aspects of the Immune System that Significantly Impact Brain Function

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Abstract

The conditions required for effective immune responses to viral or bacterial organisms and chemicals of exogenous origin and to intrinsic molecules of abnormal configuration, are briefly outlined. This is followed by a discussion of endocrine and environmental factors that can lead to excessive continuation of immune activity and persistent elevation of inflammatory responses. Such disproportionate activity becomes increasingly pronounced with aging and some possible reasons for this are considered. The specific vulnerability of the nervous system to prolonged immune events is involved in several disorders frequently found in the aging brain. In addition of being a target for inflammation associated with neurodegenerative disease, the nervous system is also seriously impacted by systemically widespread immune disturbances since there are several means by which immune information can access the CNS. The activation of glial cells and cells of non-nervous origin that form the basis of immune responses within the brain, can occur in differing modes resulting in widely differing consequences. The events underlying the relatively frequent occurrence of derangement and hyperreactivity of the immune system are considered, and a few potential ways of addressing this common condition are described.

Keywords: Neurodegeneration: Neuroinflammation, Immune, Microglia, Astroglia, Macrophage, Aging

1. Background

The immune system is a complex and sophisticated means of detecting aberrant macromolecules and promoting their dissolution or removal. This precision allows an effective shield against invasive pathogenic organisms and also enables removal of endogenous cells that are damaged or abnormal. The homeothermic nature of mammals ensures that protein structures are maintained in a relatively consistent configuration, in contrast to cold-blood phyla where these configurations can flux considerably with changing external temperature.

This constancy allows the immune system to be especially selective and sensitive. As is often the case, conferred biological benefits are also accompanied by a number of attendant hazards.

This review is intended to briefly describe some of the adverse effects that inevitably accompany the highly intricate immune system which relies on efficient interaction of a large number of separate components. The immune system on occasion, lacks the capacity to effectively down-regulate and terminate immune responses at the cessation of a crisis, and this inability is especially pronounced in the case of the central nervous system. The especial vulnerability of the nervous system to aberrant immune performance forms the core of many intractable neurological diseases. This tendency to prolong activity beyond its useful applicability also worsens with aging (Bektas et al., 2018). The basis for this malfunction is involves failure of some of the key criteria for effective immune functioning. The increasing lifespan together with exposure to a growing range of xenobiotic agents may in part account for extended age-related inflammatory events. These are a few means of minimizing their adverse effects that include pharmacological strategies together with relatively simple dietary and modifications of lifestyle.

2. General Attributes of Immune Mechanisms

2.1. Decisive features of immune responses

2.1.1 Intensity

Effective immune functioning depends on a good degree of discrimination by immune competent cells. This must allow for precise targeting of aberrant endogenous molecules and species associated with harmful organisms of exogenous origin. Sometimes, with time, there is an increasing strength of the immune response and this can become harmful, leading to allergic reactions. Conversely, certain environmentally prevalent toxic agents are known to weaken the immune system (Kravchenko et al., 2015). When the strength of the immune response has been compromised, adverse outcomes can include lack of a positive response to infectious

agents. In addition, failure of immune surveillance to recognize and remove abnormal cells can allow their survival and multiplication, leading to an elevated risk of cancer.

2.1.2. Specificity

For a useful immune response, the molecular species addressed must remain well focused without any significant drifting of identification of the target of the attack. However, another deleterious tendency of deteriorating immune function is a decline in the precision of the goal of the response.

Haptens are low molecular weight materials that are not immunogenic but can bind to endogenous proteins which can then become immunogenic. A characteristic disorder associated with such a response is contact dermatitis. Certain drugs and antibiotics can also act as haptens. An antibody may ultimately be produced that is cross reactive with the unmodified parent protein, and this can lead to an auto-immune attack drug-induced form of lupus erythematosus. Systemic lupus erythematosus is a severe disease in which the immune system is both inaccurate and hyperactive, attacking and damaging a range of organs. The central nervous system (CNS) can also be involved with neuroinflammatory changes (Duarte-Delagardo et al., 2019). Other autoimmune diseases may target on a single tissue in a more limited and specific manner (Fig. 1). These include Type 1 diabetes (involving beta cells within the pancreas), Rheumatoid arthritis (cartilage damaged), multiple sclerosis (myelin sheath of neurons attacked), myasthenia gravis (acetylcholine receptors at the neuromuscular junction ablated), most cases of Addison's disease (outer layers of adrenal cortex involved), Grave's disease (thyroid gland), pernicious anemia (intrinsic factor producing cells of the stomach), inflammatory bowel disease (cells of the digestive tract). The causal basis of these autoimmune disorders is generally unknown. A major increase in the strength of immune responses is often associated with a weakening of the degree of specificity.

2.1.3. Persistence

Restricting the period of activity of immune responses is important for their constructive and efficient functioning. Most crises where immune reactions are advantageous

and fully beneficial to an organism, are transient in nature. The inflammatory reaction to infection involves activation of transcription factors such as NF-kB leading to production of inflammatory cytokines and recruitment of macrophages. This facilitates destruction of invading organisms and removal of dead cells. When infectious entities or damaged cells are successfully disposed of, the healthy immune system then returns to low level surveillance. Regrettably however, this is not always the case. After provocation by a stimulus, immune activity often has difficulty is subsiding to levels existing before the appearance of a triggering factor. Those same processes that are valuable in engaging and blocking pathogens and cell variants, if excessively extended, can cause serious harm if continued in a protracted manner. Such persistence and failure to terminate responses may underlie several of the chronic immune disorders mentioned above.

An explanation for some situations involving a chronic inflammatory state, is the presence of inorganic materials that cannot be resolved by the immune system. This is the situation in lung disease such as silicosis or asbestosis. Here the inflammation that is caused initially by crystalline mineral particles. Since they are similar in size to bacteria, leukocytes will respond to inflammation and will attempt to ingest these particles, and this leads to their death which signals other leukocytes to aid in countering what is perceived as an infection. Fibroblasts are also recruited leading to fibrosis. Since the mineral particles cannot be cleared by these cells, they invoke chronic inflammatory events and an irresolvable site of irritation, eventually leading to infiltration of tissues with fibrotic material. In the absence of any arrest of these processes, a persistently developing disease state emerges and continues long after the original exposure to the mineral particles (Leung et al., 2012). It may be that a parallel inability to effectively clear amyloid plaques within the CNS accounts for the excess inflammation associated with Alzheimer's disease (Clayton et al., 2017).

2.2. Inappropriate continued activity of the immune system

The intricacy and subtlety of the mammalian immune system has resulting in the emergence of many undesirable and harmful side effects. Current hygienic and medical practices together with an increasingly urban life style, have resulted in a diminished challenge

of exogenous pathogenic organisms. However, this has coincided with the emergence of a range of novel allergens and hapten-forming materials. The prevalence of several common auto-immune diseases including multiple sclerosis, systemic lupus erythematosus (SLE), and type 1 diabetes mellitus has been rising (Parks et al., 2014). Many types of cancer are also likely to involve chronic inflammation (Hunter, 2012). Since the development of persistent inflammation, often of idiopathic origin is increasing, it is crucial to endeavor to identify those factors that may underlie this. Two of these features are related to the onset of increasing insensitivity to key regulatory hormones, insulin and glucocorticoids such as cortisol.

2.2.1. Insulin

The development of resistance to insulin is characteristic of Type II diabetes, and metabolic syndrome (Saltiel and Olefsky 2017). Failure of tissues to respond to insulin results in their not removing glucose from the circulation leading the hyperglycemia. This is often causal to metabolic syndrome, involving, obesity, hypertension, and high levels of circulating cholesterol (Balakumar et al., 2016). These defects can be promoted by M1-polarized pro-inflammatory macrophages (Castoldi et al., 2016). Although obesity can lead to diabetes, the relation between insulin resistance and obesity seems to be interactive rather than one factor being clearly causal to the other with each being able to potentiate the other. Both disorders and also metabolic syndrome are characterized by low grade but persistent inflammation (Frydrych et el., 2018). Type II diabetes has global effects and is associated with increased risk of cognitive impairment and of Alzheimer's disease (de la Monte et al., 2015). This likely due to impaired responsivity of the brain to insulin and mitochondrial dysfunction (De Felice and Ferreira, 2014, Sripetchwandee et al., 2018). Normal aging has been correlated with increasing unresponsiveness to insulin, and the conservation of responsivity to insulin sensitivity is associated with familial longevity (Kullmann et al., 2016).

2.2.2 Glucocorticoids

The inflammatory response is frequently terminated by the action of glucocorticoid hormones (Cohen et al., 2012). However, prolonged activation of glucocorticoid receptors can

lead to their decreased sensitivity to steroids. This insensitivity can reduce the normal capacity of glucocorticoids to inhibit inflammatory activity (Bekhbat et al., 2017). Such suppression of glucocorticoid regulation can also be promoted by extended psychological stress (Stark et al., 2001). It has been suggested that persistently excessive levels of glucocorticoids lead to glucocorticoid resistance, and may form the basis of neuroinflammatory priming in the aging brain (Fonken et al., 2018).

2.2.3 Aging and the senescence-associated secretory profile

Aging is commonly characterized by the presence of chronic, low-grade inflammation even in the absence of apparent infection (Franceschi and Campisi, 2014). This is combined with increasing incidence of widespread pathological states including obesity, diabetes, and heart disease. The root of this may relate to the characteristic senescence-associated secretory profile (SASP) of aged cells with an arrested cell cycle. This profile incorporates discharge of a range of pleiotropic inflammatory cytokines such as interleukin-6 (IL-6) (Kennedy et al., 2014). This SASP profile, can cause aging to be connected with high levels of inflammation that are unrelated to an exogenous stimulus of immune activation. Rather than being protective, the SASP spectrum promotes angiogenesis, cell proliferation, cancer invasiveness, atherosclerosis and neurodegeneration (Rea et al., 2018), a reversal of healthy immune function.

2.2.4 Environmental factors

It has been proposed that increased incidence of inflammation-related disease is largely due to the increased range of novel man-made chemicals that are present in the environment and in foods (Schmidt, 2011, Lerner and Matthias, 2015). Such xenobiotic factors of anthropogenic origin may relate to age-related elevated basal levels of inflammation. Metal-containing airborne particulate matter can effect upregulation of inflammation related genes within the CNS (Ljubimova et al., 2018) and such air pollution is very prevalent in many urban centers. A wide range of lifestyle and dietary choices together with other aspects of modern urban life may also contribute to chronic, systemic inflammatory processes (Egger and Dixon, 2014). An association has been made between the extent of exposure to several

environmental contaminants and the prevalence of Alzheimer's disease (Yegambaram et al., 2015).

Normal aging involves remodeling of the chromatin and distinctive epigenetic changes in the patterns of DNA methylation and in the non-coding miRNA profile. Dysfunctional epigenetic events play a causal role in various neurodegenerative processes (Lardenoije et al., 2015).

Overall, the immune system has many problematic aspects and as these negative features become more pronounced with age, they may gradually prevail over the beneficial properties of the immune system. While misguided immune activity may target specific organ systems, liberation of circulating factors such as inflammatory cytokines can lead to more broad organ involvement. This can jeopardize the integrity of remote tissues (Bernardi et al., 2015), including the nervous system (Solas et al., 2017).

In summary, the critical features of immune responses described above, all tend to flow toward a less beneficial balance point with age. Specificity is reduced, persistence is excessively prolonged and while the intensity of the response to authentic immune challenges is more inappropriate, despite elevated levels of inflammation.

3. The Immune System and the Brain

3.1. Susceptibility of the nervous system to prolonged systemic immune activity

Immune cells regulate many aspects of the nervous system. This occurs from the very start of ontogeny, and includes the pruning and elimination of neurons and their synapses during development as well as the subsequent organization of neuronal plasticity throughout the lifespan. Interactions between immune cells and the nervous system are bidirectional and coordinated so as to optimize somatic responses to infectious pathogens (Dantzer, 2018).

The adult central nervous system is partially protected by the blood-brain barrier. The endothelial cells of cerebral capillaries are coupled by tight junctions, leading to restricted the transfer of many high molecular weight materials. The idea that the brain thus has an "immunologically privileged" insulation from the systemic immune system has been extensively

revised and diminished in recent years, especially since the discovery of the meningeal lymphatic (glymphatic) system (De Mequita et al., 2018). While the access of immune cells to the brain is limited, some immunocompetent cells are able to traverse the blood brain barrier and take up residence in the brain. Microglia are the innate immune cells, resembling macrophages, that are normally present in the brain. However, single-cell RNA sequencing has provided results suggesting that some of these are derived from systemic monocytes (Goldman et al., 2016, Ginhoux and Garel, 2018). While infiltrating monocytes come to closely resemble intrinsically resident microglia, they may be functionally different and more liable to promote autoimmune attack on nervous tissue (Li and Barres, 2018). Thus, peripherally derived macrophages infiltrating into the brain underlie the onset and continuation of repeated social defeat-induced anxiety like behavior in mice (Wohleb et al., 2014). On the other hand, native resident microglia often act in a more supportive manner such as promotion of remyelination in multiple sclerosis (Lloyd et al., 2017). Although the proportion of cerebral microglia that are of systemic origin, derived from monocytes, is elevated in some neurodegenerative diseases, it has been proposed that such infiltrating cells may have distinctive beneficial qualities(London et al., 2013).

Other means by which a general inflammatory process may infiltrate the brain from the periphery include afferent signaling through the vagus nerve, and by way of disease-effected weakening of the brain's barrier systems (Kempuraj et al., 2017). Necrosis induced by radiotherapy of brain tissue can also lead to infiltration of inflammatory macrophages (Furuse et al., 2015). Several studies have reported that induction of systemic inflammation can produce many changes reminiscent of neurodegenerative disease in the brain which may involve a secondary excessive microglial response (Cunningham, 2013). By this means chronic inflammatory diseases relating to a single organ system, have the potential to augment the onset and progression development of several age-related neurological diseases. Persistent systemic inflammatory conditions, such as atherosclerosis, diabetes, cancer, sepsis and obesity have been associated with increased risk of a variety of neurological disorders including stroke (Drake et al., 2016), Alzheimer's disease (Holmes 2013), and Parkinsonism (Qin et al., 2007), as well as schizophrenia (Beumer et al., 2012), depression (Dowlati et al., 2010), and autism (Li et

al., 2009). All of these CNS disorders have been reported as being accompanied by neuroinflammation, and consequently, the use of anti-neuroinflammatory therapies has often been advocated as an adjunct in the treatment of systemic disorders (Kern et al.2016, Kohler et al., 2016, Meneses et al., 2019). In the case of stroke, the ischemia that initially follows can lead to a peripheral inflammatory response, followed by compensatory immunosuppression. This latter event can then increase susceptibility to infection and result in elevated mortality. Some of the interactions that link the immune responses of the brain to those taking place within the entire organism are illustrated in Figure 1.

Overall, measures of brain aging and dementia risk factors are related to the extent of systemic inflammation and this rises with age (Corlier et al., 2018). A striking example of the general immune system and that of the brain, is the consequence of a single systemic injection of lipopolysaccharide (LPS). This caused levels of the inflammatory cytokine TNF-α to be elevated in many organs. However, while these values returned to normal within a week in most tissues, TNF–α remained elevated in brain for over 10 months. This was associated with microglial activation and neurodegenerative changes in the brain (Qin et al., 2007). This report well illustrates the incapacity of the brain to rapidly restore homeostasis after an inflammatory shock. Systemic inflammation can worsen behavioral shortcomings in both aged animals (Chen et al., 2008) and in humans with neurodegenerative disease (Murray et al., 2012). The prolonged maintenance of adverse experience by the nervous system could underlie this. Reactivation of quiescent lesions by LPS in the EAE model of multiple sclerosis reveals that distant inflammatory events can enable renewed progression of indolent brain lesions (Moreno et al., 2011).

Another means by which disease states in non-nervous tissues can transmit pathological events to the brain despite the limited access granted by the blood brain barrier, may involve subcellular cytoplasmic vesicles called exosomes. Exosomes are extracellular vesicles that are released from cells upon fusion with the plasma membrane. This liberates vesicles into the extracellular fluid from whence they can travel widely. They contain a large range of macromolecules. miRNAs are an important part of their cargo. By transport of their contents into other cells, exosomes may enable the dissemination and progression of several

diseases. Migration into the brain, of exosomes in serum derived from LPS-treated mice, results in inflammatory responses and gliosis (Li et al., 2018). Such vesicles can carry immune-activating information across the blood brain barrier, in the absence of inflammatory molecules (Villaseñor et al., 2019).

Table 1 summarizes some of the disorders, both of systemic and of nervous origin, that can be associated with elevated levels of inflammation in the nervous system. The causal sequence of these correlations is not always obvious. It should be borne in mind that neuroinflammation is not only a result of some wide-ranging diseases encompassing the whole organism, but it is bi-directional in that it can also be the cause of such diseases. An example of this is the evidence that inflammation within the CNS can lead to hypertension (Haspula and Clark, 2018).

3.2. Role of macrophages, microglia and astroglia

3.2.1. Polarity of activated immune cells

Macrophage and microglial activation has been loosely classified as proceeding in one of two opposite directions. The M1 phenotype is a pro-inflammatory state, in which macrophages and microglial cells produce and release reactive oxygen species and inflammatory cytokines such as tumor necrosis factor-α (TNF-α)and interleukin 6 (Il-6). The M2 state, is not inflammatory and is engaged in the production of anabolic factors, including brain derived neurotrophic factor (BDNF) (Tang and Le, 2016). In the normal CNS microglia may be polarized toward a more M2 phenotype, but with inflammation, these cells express M1 markers. Neither of these expression states is intrinsically harmful, but unbalanced overemphasis of M1 together with diminution of M2 markers may initiate destructive events. For example, promoting a more M2 configuration of microglia can improve functional recovery following traumatic brain injury (Loane et al., 2014) while induction of M1 polarization with lipopolysaccharide results in repression of telomerase-associated genes implying cell senescence (Kronenberg et al., 2017). Both M1 and M2 configurations of macrophages and probably microglia possess phagocytic activity, and this can be associated with targeted cell or

micro-organism removal, or with overall tissue repair and remodeling events (Boche et al., 2013). Each of these states represents a transition from a relatively dormant cell, but the outcomes of each type of activation are very different.

At the onset of AD, microglia are predominantly activated as the M2 form while as the disease progresses, the activation is more directed toward the inflammatory M1 form (Shen et al., 2018). This type of transition is also found following ischemic stroke (Wang et al., 2018). The immune response to acute cerebral ischemia is a major factor in determining the outcome following acute ischemic stroke (Anrather and Iadecola, 2016). However, in glial tumors where inflammation is low and anabolic processes predominate, the presence of markers of the M2 phenotype predominates over markers for M1, and this facilitates tumor progression (Sasaki, 2017). Since a broad spectrum of intermediate states between M1 and M2 phenotypes exists, a simple separation into these two classes is insufficient. Nevertheless, this division albeit imprecise can be useful in outlining the characteristics generally associated with each cell type (Table 2).

Neuroinflammation is likely an important factor in accounting for age-related cognitive decline (Bettio et al., 2016). In a clinical study, macrophages derived from patients with mild cognitive impairment (MCI), were unable to phagocytize and degrade amyloid-β1 - 42 (Aβ). Dietary administration of ω-3 fatty acids, antioxidants, vitamin D3, and resveratrol together, restored the ability of macrophages to clear amyloid and phagocytose unfolded proteins and slowed down the rate of cognitive decline. This was accompanied by a phagocytic macrophage type, whose expression profile reflected a combination M1 and M2 characteristics (Fiala et al., 2018). Microglia cannot simply be described as either dormant or activated as they are very responsive to the surrounding milieu which can rapidly alter the spectrum their gene expression profile in a complex rather than a binary manner (Gosselin et al., 2017).

Generally, there is clear evidence that the switch of microglia from the M1 to M2 phenotype is able to lessen adverse changes in animal models of AD, by attenuation of inflammation (Yao and Zu, 2019), and this has been associated with improved cognition (Zhu et al., 2016). Alternatively activated microglia in the M2 form are largely involved with tissue repair, phagocytosis of misfolded proteins and dead cells, while the classical M1 configuration

predominates in neurodegenerative states (Manchikalapudi et al., 2019) and can promote protein misfolding (Tang and Le, 2016). A range of pharmacological strategies have been suggested in order to effect the transition toward the M2 state (Yao and Zu, 2019). While treatments for neurodegenerative disease may attempt a polarization toward the M2 form of microglia, therapy for glioma is likely most beneficial when directed toward inducing a M1 form (Song and Suk, 2017). Rebalancing the equilibrium of microglial polarity toward either anabolic or inflammatory events can have significant therapeutic relevance (Kanazawa et al., 2017).

3.2.2. Microglial ablation studies

The ability to selectively ablate microglia by pharmacological means has led to much recent work on this strategy involving their transient depletion. While this is a very active area, consensus has not yet been reached on whether the role of microglia is largely beneficial or detrimental.

In the study of neurodegenerative or brain trauma, reports concerning the advantageous nature of glial ablation predominate. Thus animal models of Alzheimer's disease (AD) respond well to elimination of microglia, exhibiting diminished formation of amyloid plaques (Spangenberg et al., 2019). As a result, pharmacological removal of microglia, followed by repopulation has been suggested as a potential therapy for a variety of neurodegenerative disorders (Han et al., 2019). Microglial removal has also been described as beneficial in a variety of conditions including reduced severity of postoperative inflammation (Feng et al., 2017), and a diminished response to acute ethanol withdrawal (Walter and Crews, 2017).

However, there are also reports that conflict with the concept that microglial removal confers benefits. In another mouse model of AD, ablation of resident microglia allowed penetrance of peripheral macrophages in to the brain and the emergence of increased expression of inflammatory genes and a much more pro-inflammatory milieu (Unger et al., 2018). The ablation procedure also blocked host defenses against prion disease (Carroll et al., 2018) and against picornavirus infection of the brain (Sanchez et al., 2019). Evidence for the useful role of microglia includes a report that their depletion exacerbates post-ischemic inflammatory damage within the brain (Jin et al., 2017). Finally, effecting repopulation of

microglia subsequent to their depletion in aged mice reverses cognitive and morphological defects (Elmore et al., 2018).

The subtle nature of microglial functioning has yet to be clarified. While it is obvious that microglia play an essential supportive role in nervous tissue, they appear under some common circumstances, to undergo pathological transformation to a form where they enhance and promote disease processes. Perhaps the best clue to resolving these apparently contradictory findings, comes from the report of Garcia-Agudo et al., (2019). This group found that while microglia depletion transiently benefitted genetically induced brain inflammation, a residual surviving microglial species which was aggressively inflammatory and destructive, soon expanded. This led to no long term improvement whatsoever in treated mice. Detailed investigation of the variety of microglial species and the kinetics of their proliferation in response to an altered environment, are a complex challenge but may explain the reason underlying the many inconsistent reports on this topic.

3.2.3. Astroglia

Brain inflammation is also enabled by astroglia which respond to adverse events in the CNS by undergoing reactive gliosis, and displaying inflammatory markers such as glial fibrillary reactive protein (GFAP)(Norden et al., 2015). There is extensive supportive interaction between microglial and astroglial activity, and with age (Crotti and Ransohof, 2016), this leads to progressively increasing basal levels of cerebral basal inflammation (Primiani et al., 2014). This increase is especially pronounced in the presence of neurodegenerative disorders (Kabba et al., 2018).

Astrocytes resemble microglia in that they have both a positive and an undesirable role in maintaining cerebral function. They can clear dead cells (Lui et al., 2018), and form a border between neural cells and other tissues such as blood vessels and the meninges. However they are able to act as viral reservoirs, and may thus prolong viral in the brain (Li et al., 2016). In addition, astrocytes are capable of apparently unprovoked reactive gliosis that involves enhanced production of inflammatory cytokines, and reactive oxygen species, changes that can

interfere with neuronal structure and function. In addition to AD, several other neurodegenerative disorders are associated with astroglial activation, including Parkinson's disease (PD) and multiple sclerosis (MS) (Stephenson et al., 2018). Astroglia are also capable of expressing anti-inflammatory properties, and this duality may account for the waxing and waning nature of MS (Sofroniew, 2015). Inhibition of reactive astrogliosis has been reported to intensify beta-amyloid peptide deposition and to increase levels of inflammation in a mouse model of AD (Kraft et al., 2013). Conflicting findings related to the role of astroglia in neurodegenerative disease may also reflect their capacity to exist in several activated states with strikingly different properties (Liddelow and Barres 2017). Induction of neuroinflammation with lipopolysaccharide leads to formation of a detrimental type of reactive astrocyte, while the reactive astrocytes generated after ischemia, have a gene expression profile reflecting more protective qualities (Zamanian et al., 2012). These have been termed A1 and A2 respectively, paralleling the M1/M2 distinction of microglia (Lidelow and Barres, 2017). On the whole, reactive astrocytes seem predominantly deleterious in AD and their suppression offers a promising therapeutic strategy (Ceyzériat et al., 2018).

3.2.4. Micro-RNAs

In recent years, micro-RNAs (miRNAs) have emerged as major cytoplasmic regulators of post-transcriptional activity of their corresponding messenger RNAs. A single miRNA may act on many different mRNA targets (Friedman et al., 2009) and this breadth makes these molecular species particularly powerful in control of biological function. miRNAs play an important role in influencing macrophage/microglial activity and thus as critical modulators of immunity and inflammation. miR-124 facilitates downregulation of indices of the M1 phenotype such as the inflammatory cytokines IL-6 and TNFα while M2-linked markers such as neurotrophic and growth factors are upregulated (Ponomarev et al., 2013). miR-124 is the most highly expressed miRNA in neurons and is also present in large amounts in immune cells (Qin et al., 2016). Additionally, miR-124 appears to be essential for the initiation and maintenance of the M2 phenotype (Qin et al., 2016) and is also important in maintenance of cerebral vasculature and inhibition of neuronal apoptosis (Che et al., 2019, Li et al., 2019). In contrast,

miR-155 is oriented toward promotion of the microglial polarization toward a more inflammatory posture (Guo et al, 2019). Transcriptome analysis of microglia from models of neurodegenerative diseases often exhibit heighted levels of both M1 and M2 markers together (Sarlus and Heneka, 2017).

Whether or not the activity of a specific miRNA is supportive or harmful is very dependent on the target issue. For example miRNA-21 administration can mitigate the magnitude of brain injury by inhibition of inflammation and apoptosis. Thus it has been suggested as a possible treatment for stroke (Ge et al., 2016). On the other hand, this same miRNA is implicated in the promotion of neoplastic transformation, angiogenesis support and growth of glioma (Chai et al., 2018).

3.3. Potential therapeutic directions

A wide range of pharmacological and phytochemical tactics are being investigated to both to understand the basis of, and to devise means of mitigating the age related progression of inflammatory disorders. Three possible strategies are listed:

3.3.1 Mitochondrial protection

Chronic inflammation leads to impaired functioning of the mitochondrial tricarboxylic acid cycle which leads production of excess free radicals. This can be mitigated by dimethylfumarate which exerts an anti-inflammatory effect by both inhibiting mitochondrial aerobic glycolysis (Kornberg et al., 2018), and activation of the nuclear factor erythroid 2–related factor 2 (Nrf-2) signaling pathway (Giustina et al., 2017). Dimethylfumarate administration has been found useful as a means of reducing immune responsivity, and has clinical utility in the treatment of multiple sclerosis (Wingerchuk and Weinshenker, 2018).

3.3.2 Slowing onset genetic changes characterizing aging

Another tactic could be to develop means to retard the changes in gene expression and miRNA profile taking place with aging. These changes are tilted toward increased

manifestation of inflammatory gene activity (Victoria et al., 2017, Sharman et al., 2004). These changes could be remedially addressed by use of inexpensive agents such as melatonin, which has been shown to reverse many of the age-related changes modification of the gene expression profile, especially those relating to immune activity (Bondy, 2018). Melatonin declines rapidly with age (Lahiri et al., 2001a) but cortical levels can be elevated by dietary administration. Such treatment can also reduce levels of amyloid β–peptides in an experimental animal model (Lahiri et al., 2001b).

3.3.3 Reduction of glycemic potency of diet and increase of physical activity

A marked association between diets with a high inflammatory potential and less favorable measures of brain and cognitive health, has been made among the elderly (Gu et al., 2018). The rapid evolution of the incidence of immune-mediated inflammatory diseases among immigrants, further suggests a role for non-genetic factors and gene-environment interactions (Agrawal et al., 2019). It then follows that appropriate environmental modifications could be promptly useful in reducing the prevalence of these disorders. This is consistent with the promotion of a suggested ketogenic diet in order to broadly control systemic inflammation (Dupuis et al., 2015, Puchalska and Crawford, 2017). The utility of regular exercise in attenuating age-related inflammation has similarly been frequently attested to (Garatachea et al., 2015). These changes could be effected readily without the necessity for development of specific new drugs and would be low cost. It has been advocated that this dietary approach may be of especial value in the treatment of neurodegenerative diseases (McDonald and, Cervenka, 2018). The development of more sophisticated means to maintain the selectivity and efficiency of immune responses with senescence, is a growing medical concern and a challenge for the future. However this dietary approach is limited only by the ability to convince people to make relatively simple changes, but that demand a degree of determination to modify their routines.

3.3.4 A role for immunotherapy

The potential for immunotherapy for moderation of senescence-related or neurodegenerative events has been widely studied but overall, success in this area remains

elusive. The development of antibodies specific for undesirable peptides, while most promising in animal models, has not proved as useful in clinical trials as hoped, and has sometimes led to serious undesirable side effects (Wisniewski and Goñi, 2015, Valera et al., 2016). However a less focal approach involving intravenous administration of general immunoglobulins (IVIG) has been more promising and has minimal toxic sequelae (Vitaliti et al., 2017, Thom et al., 2017). Nevertheless, this area is currently being intensively investigated and in dynamic flux, thus offering much hope in the future.

4. Conclusion

The listing of the pathological consequences of excess immune activity, should not obscure the fact that the immune system has been maintained and enriched with time by evolutionary processes, indicating its great value. The issue then arises as to why then there are so many instances of aberrant and excessive inflammation. There are several possible explanations for this, many of which relate to the prevailing life style. The way of life today often contains less physical activity and a greater dietary abundance than over the large timespan of human existence. These features can account for the prevalence and likely increase of many disorders with an inflammatory component. But perhaps the most significant factor to be considered, is the increased lifespan of modern times. This prolongation beyond reproductive years implies that no further evolutionary pressures can be exerted in later life. Thus any aberrant metabolism of the elderly cannot be amended by selective forces. The immune system functions efficiently in the young, but cannot respond as successfully to the new demands placed on it by extended survival. It is noteworthy that the large majority of disorders including an undesirable inflammatory component, become increasingly pronounced with age. All three of the distinctive features of immune responses described above, become less effective with age. The efficiency of the immune response may be gradually, compromised by the combination of a loss of selectivity together with protracted inflammatory activity. In this manner, the adverse effects of immune activity gradually become more pronounced and persistent and slowly displace the many positive features of immune defense. However, there are accessible means of moderating this inevitable deterioration that could readily be acted

upon. It is urgent that relevant information be more generally directed to a more extensive audience.

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Fig. 1

Representation of factors by which systemic immune activity may lead to prolonged inflammatory responses in thrcentral nervous system

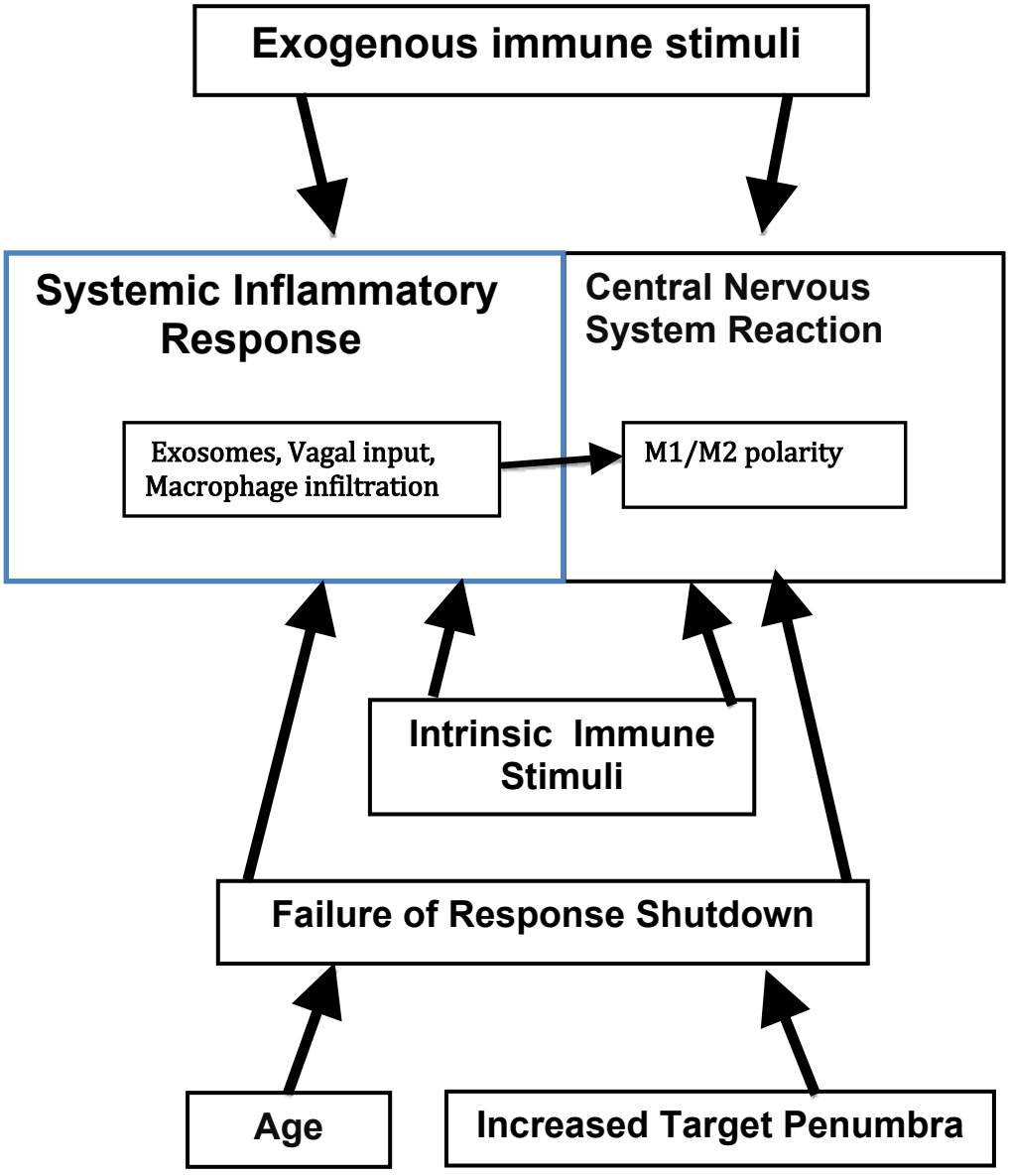

Table 1.

Adverse health conditions associated with neuroinflammation.

Disturbances of Nervous Origin	
Neurodegenerative disease (AD, PD, HD, MS, ALS)	Stephenson et al., 2018
Brain irradiation	Furuse et al., 2015
Traumatic brain injury	Corrigan et al., 2016
Stroke	Anrather and Iadecola, 2016
Depression	Kohler et al., 2016
Autism	Kern et al., 2016

Disturbances of Systemic Origin	
Aging	Bettio et al., 2017
High fat diet	Spencer t al., 2017
Abnormal gut microbiota	Russo et al., 2018
Inhalation of particulate matter	Ljubimova et al., 2018
Peripheral inflammation	Demers et al., 2018
Diabetes	Muriach et al., 2014
Hypertension	Haspula et al., 2018
Lupus erythematosus	Makay, 2105
Sepsis	Meneses et al., 2019

Table 2.
Comparison of properties of macrophages/microglia at the two poles of differing states of activation.

Promoted by M1 type cell polarization (classical activation)	**Promoted by M2 type cell polarization (alternative activation)**
Bacteriocidal events promoted	Anabolic, Reconstructive processes in injured tissues
Attempt to phagocytose tumor cells, promotion of T-cell responses	Tumor progression, angiogenesis and resistance to chemotherapy enhanced
Inflammatory factors produced	Anti-inflammatory cytokines produced
M1 polarity elevated rapidly after injury, removal of dead cells	Delayed increase of M2 type after injury, repair initiated
Diabetes, insulin resistance elevated	Insulin sensitivity restored, plasma glucose levels regulated
Obesity	Adipose tissue homeostasis maintained
Enriched in atherosclerotic plaques	Regression of atherosclerosis
Induced by misfolded proteins	Clearance of misfolded proteins, and beta amyloid
Promotion of elevated inflammation, apoptosis, neurodegenerative disease Phagocytosis	Neuroprotection after traumatic brain injury. Tissue remodeling after stroke Phagocytosis
Repression of telomere complex genes	Upregulation of genes related to bioenergetic metabolism

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